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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/359,260	07/22/1999	ROBERT L. CAMPBELL	P3250	2590

26253 7590 10/31/2005

DAVID W. HIGHET, VP AND CHIEF IP COUNSEL
BECTON, DICKINSON AND COMPANY
1 BECTON DRIVE, MC 110
FRANKLIN LAKES, NJ 07417-1880

EXAMINER	
DEJONG, ERIC S	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/359,260	CAMPBELL ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73,76,82-127,131,132 and 134-138* is/are pending in the application.

4a) Of the above claim(s) *1-73 and 96-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76, 82-95, 131, 132, and 134-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/23/2005; 7/29/2005; 8/26/2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 August 2005 has been entered.

TITLE

Applicants submission of a new title for the instant application is acknowledged.

Claim Rejections - 35 USC § 112, First Paragraph

The previous rejection of claims 76, 82-93, 95, 131, 132, and 134 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 76, 82-95, 131, 132, and 134-138 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. This rejection is newly applied and necessitated by amendment to the instant claims.

The independent claims 135-138 each recite a step of "constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design". See lines 11 and 12 of claim 135, lines 11 and 12 of claim 136, lines 11 and 12 of claim 137, and lines 11 and 12 of claim 138. However, the instant claims only recite a step of "performing a space-filling design of the parameterized peptides", a step that is performed on all molecules and does not result in segregating the predetermined set of peptides into "identified" or not-"identified" groupings. Therefore, there claims omit an essential step of identifying a plurality of first test peptides by means of a space-filling design that would provide a sufficient antecedent basis for the claimed limitation of "first peptides identified using the space-filling design".

Claim 84 recites the limitation "sequence specific parameter" in line 3 of the instant claims. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 76, 82, 87-95, 131, 132, and 134-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Ostrem et al. This rejection is maintained and reiterated from the previous Office action.

The instant claims are drawn to methods of identifying a peptide with a desired activity having an indicia that satisfies a test requirement comprising the steps of identifying a predetermined set of peptides, parameterizing the predetermined set of peptides by determining for each peptide a first whole molecule parameter and a second parameter that is dependent on the specific order of constitutive subunits within each peptide, performing a space filling design model of the parameterized peptides, constructing a first test peptide library comprising a plurality of the first test peptides identified using a space-filling model, determining an activity of said plurality of first test peptides, measuring the indicia of said activity, deriving a quantitative relationship between said indicia of said activity, and said first and second parameters, calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship, setting a test requirement having a test indicia range, selecting a second test peptide library different from said first test peptide library,

measuring the indicia of each second test peptide, and identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

[Claims 94, 95, 132, 134, 135, 137, and 138]: Ostrem et al. sets forth a procedure for drug discovery by the preparation of a octamer combinatorial test peptide library in order to identify leads compounds therein (identifying a predetermined set of peptides). See Ostrem et al., at least Abstract and page 1054, column 1, first paragraph. Ostrem et al. discloses the determination of a combinatorial peptide library, wherein the peptides are 8 amino acids in length and have been evaluated as having a potency of 4 to 15 μM and retain an unusual selectively for factor Xa over thrombin. Ostrem et al. shows the instantly claimed determination of a first whole molecule parameter, a second parameter that is dependent on the specific order of constitutive subunits, and constructing a first test peptide library comprising a plurality of first test peptides identified using a space-filling design (see Ostrem et al., at least Abstract and page 1053, column 1, line 1 through column 2, line 32). Further, the measurable and "unusual selectivity" of peptides to bind factor Xa also reads on the claimed measuring the indicia of an activity of a plurality of first test peptides. The described procedures for testing a family of combinatorial peptides of 8 amino acids in length to bind factor Xa and level of potency reads on the claimed determination of a relationship between an indicia of activity, a first parameter, and a second parameter.

Ostrem et al. further sets forth four separate assays that are described and performed on peptides identified from an initial set of combinatorial octamer peptides, wherein peptide-bound beads are separately prepared and used in each of the four

distinct assay (see Ostrem et al., page 1054, column 2, line 1 through page 1055, column 1, line 41). The selection of peptides based on the results of these assays reads on the instantly claimed limitations of setting a test requirement having a test indicia range, selecting a second test peptide library different from said first test peptide library, measuring the indicia of each second test peptide, and identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

[Claim 76]: Evaluating the potency of the octamer combinatorial peptides set forth by Ostrem et al. has been interpreted as reading on determining a relationship comprising the step of determining $y_i=f(x_{ij})$, wherein potency is the whole molecule parameter X_{ij}, i represents the number representative of octamer peptide tested, j ranges from 1 to d, and d is 1 as only one whole molecule parameters is evaluated, and y_i represents potency, the activity being determined for each octamer combinatorial peptide.

[Claim 82]: Identifying a subset of the first peptide library and, based upon their ability to bind factor Xa, using the peptides in a prothrombinase assay set forth by Ostrem et al. reads on the instantly claimed space-filling design expanding less than all of the first test peptides into their constituents.

[Claims 87-90 and 93]: The ability of test peptides to bind to factor Xa reads on the claimed activity of binding to a receptor and the claimed activity is inducement of activation of a receptor within a cell.

[Claim 91]: Ostrem et al. sets forth in the Factor Xa assay the addition of peptide stock solutions to substrate media in half-area microtiter plates, which reads on the

instantly claimed limitation of forming a plurality of culture media each containing a respective test peptide. See Ostrem et al., page 1054, column 2, lines 19-42.

[Claim 92]: Part of the disclosed library screening process includes the step of incubating destained beads with the factor Xa-SAP-inhibitor mixture. See Ostrem et al., page 1054, column 1, first paragraph. The disclosed determination of activity is interpreted as peptides being exposed to an incubation process with the inhibitor mixture set forth by Ostrem et al. reads on the instantly claimed inhibition of activation of a receptor. Further, the step of incubation reads on a step of adjusting said test requirement by a desired value for improving results of said step of selecting a new second peptide library.

[Claim 131]: Page 39, lines 7-34 of instant specification provides an exemplary embodiment of using a space-filling design wherein a particular cut-off distance for potential lead-compounds that is used to identify compounds of interest. In this example, the "distance function" that was applied was an arbitrary cut-off limit for the variability of the specific characteristics of peptide hydrophobicity and total dipole moment. Figure 4, Table 2, and pages 1056, line 1 through page 1057, column 2, line 2 of Ostrem et al. sets forth that identification of lead compounds comes from the assessing the plotted estimated values of relative activity, protein concentration, and inhibition. Further, Figure 5 and page 1057, column 2, line 4 through page 1058, column 2, line 5 of Ostrem et al. further discusses the criteria that were used to distinguish and identify novel lead compounds from amongst all compounds utilized in the investigation., which is interpreted as the application of a distance function which is

consonant with the above described example provided in the instant specification. Therefore, the above described method of identifying novel ligands by Ostrem et al. reads on the claimed limitation of a space-filling design that applies a distance function.

[Claim 136]: Page 45, lines 6 and 7 of the instant specification defines the claimed term "compound isomers" as "the group of compounds sharing common global characteristics". The procedures disclosed by Ostrem et al. utilize biotin labeled protein to attach peptides from libraries to beads, and thus produce a library of bead-bound peptides. The beads are then utilized in specific assayed for activity against purified proteins and result in the identification of peptides with a desired property, thus allowing for the specific selection of beads containing peptides of a desired property. Since the peptides attached to a bead are not constrained in any manner, the structural variability for a group of peptides is unrestrained, the peptides necessarily sample any and all alternative conformations that are specific to a given octamer sequence. As such, the disclosed procedures reads on the instantly claimed steps of expanding first test peptides into their compound isomers and performing a space-filling design on said constituent compound isomers to identify candidate peptides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 76, 82-95, 131, 132, and 134-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostrem et al. in view of Cramer 9US Patent No 6,240,374).

The instant claims are drawn to methods of identifying a peptide with a desired activity having an indicia that satisfies a test requirement as discussed above and further limiting the group that a first parameter and second parameter may be selected from.

[Claims 83-86]: As discussed above, Ostrem et al. sets forth a procedure for drug discovery by the preparation of a octamer combinatorial test peptide library in order to identify leads compounds therein. However Ostrem et al. does not fairly teach the parameterization a predetermined set of peptides using a first and second parameter selected from the groups recited in instant claims 83-86.

Cramer et al. sets forth a method of validating molecular structural descriptors that may be used to select optimally diverse subsets of molecules with a desired set of characteristics. See Cramer et al., Abstract. Cramer et al. further discloses an example wherein a library database of compounds is selected for on the basis of molecular weight and hydrophobicity.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to parameterize peptides on the basis of molecular weight and hydrophobicity, as taught by Cramer et al. used in the procedure for drug discovery as set forth by Ostrem et al. because Cramer et al. teaches that the optimizing the characteristics of compound libraries utilized in drug discover is critical for establishing a sufficiently diverse but

manageable set of starting compounds for further investigation (see Cramer, et al., column 2, lines 51 through column 3, line 67).

Response to Arguments

Applicant's arguments filed 08 August 2005 have been fully considered but they are not persuasive.

Applicants argue that Ostrem et al. does not appear to disclose or suggest a method of identifying peptides with a desired activity level as set forth in independent claim 135. Specifically, Applicants argue that Ostrem et al. ails to teach or suggest the following:

(1) Ostrem et al. does not parameterize the predetermined peptides through determination of first and second parameters,

(2) Ostrem et al. utilizes a combinatorial library and does not disclose or suggest any space-filling techniques,

(3) Ostrem et al. provides no disclosure or suggestion for deriving a quantitative relationship between the measured indicia, the first parameter, and the second parameter, and

(4) Ostrem et al. fails to suggest application of the derived quantitative relationship to calculate an estimated indicia for peptides remaining in the predetermined set of peptides.

In response to Applicants argument that Ostrem et al. does not parameterize the predetermined peptides through determination of first and second parameters,

Applicants attention is directed to the above discussion of Ostrem et al. which discloses the determination a combinatorial peptide library. The library set forth in Ostrem et al. comprises peptides of 8 amino acids in length and have been evaluated as having a potency of 4 to 15 μM and retain an unusual selectively for factor Xa over thrombin, which reads on the instantly claimed determination of a first whole molecule parameter and a second parameter that is dependent on the specific order of constitutive subunits. The evaluation of peptides having a measurable level of potency from 4 to 15 μM is interpreted as a whole molecule parameter since potency is an inherent property of each individually assayed compound. Further, the evaluation of peptides on the basis of selectivity for factor Xa is interpreted as being dependent on the specific order of constitutive subunits as the specific sequence of a given peptide under investigation is directly correlated to the functional activity for that given peptide. Therefore, applicants arguments are not found persuasive as Ostrem et al. discloses the parameterization of a family of peptides using whole-molecule and sequence-specific parameters as instantly claimed.

In response to Applicants arguments that Ostrem et al. utilizes a combinatorial library and does not disclose or suggest any space-filling techniques, it is noted that Applicants argument does refer to any definition of "space-filling" techniques from the disclosure that would exclude the construction of combinatorial library of test peptides as reading on a space-filling technique. As discussed above, Ostrem et al. discloses the construction of a combinatorial library of peptides containing a multitude of varying peptide sequences in order to investigate changes in peptide properties that can be

correlated to specific sequence changes. Thus, the combinatorial library has been interpreted as providing a space-filling model wherein variations of octamer peptides have been explored in both a sequence and conformational space context.

In regards to Applicants arguments that Ostrem et al. provides no disclosure or suggestion for deriving a quantitative relationship between the measured indicia, the first parameter, and the second parameter, Tables 1 and 2 and Figures 1 and 2 of Ostrem et al. clearly demonstrates the estimation of curves for peptides exhibiting inhibition of factor Xa activity among tested peptide sequences identified as binding factor Xa and increased potency. Therefore, Applicants argument is not found persuasive for the reasons provided above.

In regards to Applicants arguments that Ostrem et al. fails to suggest application of the derived quantitative relationship to calculate an estimated indicia for peptides remaining in the predetermined set of peptides, it is reiterated that Tables 1 and 2 and Figures 1 and 2 of Ostrem et al. clearly demonstrates the estimation of curves for peptides exhibiting inhibition of factor Xa activity among tested peptide sequences identified as binding factor Xa and increased potency. Applicants further argue that the increased potency range of the initial leads identified in the combinatorial library are measured and not calculated. This is also not found persuasive as all curves presented by Ostrem et al. were estimated from discrete measurements which were then further extrapolated (see in Figures 1-5 of Ostrem et al.). Therefore, contrary to Applicants argument, Ostrem et al. does provide a calculation of a derived relationship as set forth in the instant claims.

Conclusion

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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EDJ EDJ

14 October 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER